1: Drugs 2000 Apr;59(4):753-67

Tyrosine kinase inhibitors targeted to the epidermal growth factor receptor subfamily: role as anticancer agents.

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Abnormal cell signal transduction arising from protein tyrosine kinases has been implicated in the initiation and progression of a variety of human cancers. Over the past 2 decades pharmaceutical and university laboratories have been involved in a tremendous effort to develop compounds that can selectively modulate these abnormal signalling pathways. Targeting receptor tyrosine kinases, especially the epidermal growth factor receptor subfamily, has been at the forefront of this effort as a result of strong clinical data correlating over-expression of these receptors with more aggressive cancers. There are a variety of strategies under development for inhibiting the kinase activity of these receptors, targeting both the extracellular and intracellular domains. Antibody-based approaches, immunotoxins and ligand-binding cytotoxic agents use the extracellular domain for targeted tumour therapy. Small molecule inhibitors target the intracellular catalytic region by interfering with ATP binding, while nonphosphorylatable peptides are aimed at the intracellular substrate binding region. Compounds that inhibit subsequent downstream signals from the receptor by interrupting intracellular protein recognition sequences are also being investigated. In the past 5 years enormous progress has been made in developing tyrosine kinase inhibitor compounds with sufficient potency, bioavailability and selectivity against this subfamily of receptor tyrosine kinases. The anti-HER2 monoclonal antibody, trastuzumab, for patients with metastatic breast cancer is the first of these inhibitor compounds to gain FDA approval. However, preclinical and clinical trials are ongoing with a variety of other monoclonal antibodies, immunotoxins, and small molecule quinazoline and pyrimidine-based inhibitors. Although their cytotoxic and cytostatic potential has been proven, they are not likely to replace standard chemotherapy regimens as single-agent, first-line therapeutics. Instead, their promising additive and synergistic antitumour effects in combination with standard chemotherapeutics suggest that these novel agents will find their greatest utility and efficacy in conjunction with existing anticancer agents.

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Appendix A

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Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy.

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Increasing knowledge of the structure and function of the epidermal growth factor receptor (EGFR) subfamily of tyrosine kinases and of their role in the initiation and progression of various cancers has, in recent years, provided the impetus for a substantial research effort aimed at developing new anticancer therapies that target specific components of the EGFR signal transduction pathway. Selective compounds have been developed that target either the extracellular ligand-binding region of the EGFR or the intracellular tyrosine kinase region, resulting in interference with the signalling pathways that modulate mitogenic and other cancer-promoting responses (e.g. cell motility, cell adhesion, invasion and angiogenesis). Potential new anticancer agents that target the extracellular ligand-binding region of the receptor include a number of monoclonal antibodies, immunotoxins and ligand-binding cytotoxic agents. Agents that target the intracellular tyrosine kinase region include small molecule tyrosine kinase inhibitors (TKIs), which act by interfering with ATP binding to the receptor, and various other compounds that act at substrate-binding regions or downstream components of the signalling pathway. Currently, the most advanced of the newer therapies undergoing clinical development are antireceptor monoclonal antibodies (e.g. trastuzumab and cetuximab) and a number of small molecule EGFR-TKIs principally of the quinazoline and pyrazolo-pyrrolo-pyridopyrimidine inhibitor structural classes. The latter group of compounds offers several advantages in cancer chemotherapy, including the possibility of inhibiting specific deregulated pathways in cancer cells while having minimal effects on normal cell function. They also have favourable pharmacokinetic and pharmacodynamic properties and low toxicity, and some TKIs such as the reversible inhibitor ZD1839 ('Iressa') are now undergoing phase II to III clinical trials. In addition, the accumulation of evidence from laboratory studies strongly suggests that EGFR-selective TKIs will have synergistic effects with other antitumour agents or therapy such as cytostatic agents, conventional cytotoxic drugs and radiotherapy. As our knowledge of signal transduction pathways in cancer increases, it is hoped that further advances in this area will allow the therapeutic potential of these compounds as anticancer agents to be realised.

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Epidermal growth factor receptor tyrosine kinase inhibitors as anticancer agents.

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The epidermal growth factor receptor (EGFR)-driven autocrine growth pathway has been implicated in the development and progression of the majority of the most common human epithelial cancers, making the blockade of this growth pathway a promising anticancer therapeutic strategy. Different approaches have been developed to block EGFR activation and/or function in cancer cells. In the past 15 years, various anti-EGFR blocking monoclonal antibodies (MAb), recombinant proteins containing transforming growth factor-alpha (TGFalpha) or EGF fused to toxins, and tyrosine kinase inhibitors (TKIs) have been generated and their biological and potentially therapeutic properties characterised. One of these agents, MAb IMC-C225, a chimeric human-mouse IgG1 MAb, is the first anti-EGFR agent to enter phase II to III clinical trials in patients with cancer. Several small compounds that block the ligand-induced activation of the EGFR tyrosine kinase have been developed. Among these EGFR-TKIs, various quinazoline-derived agents have been synthesised and have shown promising activity as anticancer agents in preclinical models. ZD1839 ('Iressa'), an anilinoquinazoline, is an orally active, selective EGFR-TKI which is currently under clinical evaluation in phase II to III clinical trials in patients with cancer. Preclinical data for ZD1839 strongly support the possibility of potentiating the antitumour activity of conventional chemotherapy with agents that selectively block the EGFR.

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Developments in chemotherapy of breast cancer.

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BACKGROUND: Breast carcinoma is moderately sensitive to multiple antitumor agents. Cytotoxic combination regimens developed in the 1970s were shown to produce higher response rates and longer durations of response and survival than single-agent therapy. These regimens became the standard of care for the management of metastatic, hormone-refractory breast carcinoma, and more recently, for primary breast carcinoma. Randomized trials also have demonstrated that anthracycline-containing combinations were more effective than combinations without anthracyclines. The development of several new cytotoxic agents and novel antitumor strategies prompted this review. METHODS: The author conducted a computerized literature search of MEDLINE and CANCERLIT and also reviewed the abstracts of major oncology meetings (ASCO, American Association for Cancer Research, ESMO, and San Antonio Breast Cancer Symposium) over the past 10 years. RESULTS: Effective new cytotoxic drugs include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and capecitabine. The identification of specific molecular abnormalities (HER-2/neu or epidermal growth factor receptor [EGFR] overexpression) led to the development of targeted therapeutic intervention (monoclonal antibodies and tyrosine kinase inhibitors). Trastuzumab, a monoclonal antibody against the HER-2/neu oncoprotein, produced objective regression in 15-20% of patients with HER-2/neu-overexpressing breast carcinoma and improved the efficacy of paclitaxel. Other productive directions of therapeutic research include inhibition of intracellular signaling, interference with tumor angiogenesis, cell cycle regulation, and the development of vaccines. CONCLUSIONS: Expanded understanding of the biology of breast carcinoma led to the development of rational therapeutic interventions, many of which are currently under active clinical development.

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Epidermal growth factor receptor inhibition in cancer therapy: biology, rationale and preliminary clinical results.

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The epidermal growth factor receptor (EGFR), a growth factor receptor involved in the regulation of cellular differentiation and proliferation, is highly expressed by many tumor cells. In light of a relationship between overexpression of EGFR and clinically aggressive malignant disease, EGFR has emerged as a promising target for cancer therapy. In recent years, several molecular strategies have been explored to modulate either the EGFR itself, or the downstream signal beyond the cell surface receptor. One of the most promising current strategies involves the use of anti-EGFR monoclonal antibodies (mAbs), either alone or in combination with conventional cytotoxic modalities such as chemotherapy or radiotherapy. This review focuses primarily on recent progress in the development of anti-EGFR mAbs, and examines their potential in the treatment of cancer.

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